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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,470	08/22/2003	Ellen Chien	SYR-CATS-5002-C1	9594

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,470	CHIEN ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *18-26* is/are withdrawn from consideration.

5)☒ Claim(s) *18* is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-26 are pending and under consideration.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-18, drawn to a composition comprising a Cathepsin S (CatS) crystal and a method of making the crystal, classified in class 435, subclass 194.

II. Claims 19-26, drawn to method of determining protein structure, classified in class 435, subclass 4.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the protein structure can be determined without the crystal, e.g., in solution by NMR method, whereas the crystal can be utilized in a method to purify the protein.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with David J. Weitz on January 9, 2006 a provisional election was made without traverse to prosecute the invention of invention I, claims 1-18. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final

rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. CatS in paragraphs 189-191, Figure description of Figures 2, 3, 4, 5A, and 6, and headings of Tables 2-8 should be followed by a sequence identification number (see 37 CRF 1.821 (d)).

The disclosure is objected to because of the following informalities:

(1) The specification refers to a chemical compound as E-64, which is not a chemical name and one of ordinary skill in the art would not know what it is. Since the structure of E-64 is disclosed in the tables of atomic coordinates of Figure 3, an appropriate chemical name or a structure formula should be inserted to identify the chemical compound E-64.

(2) At page 23, paragraph 97, line 7, "□L" should be corrected.

Appropriate correction is required.

The drawing of Figure 1 is objected to because the Figure heading of SEQ ID NO: 2 is misleading. The nucleic acid shown in SEQ ID NO: 2 is that of fragment of the coding sequence of cathepsin S. SEQ ID NO: 2 is 576 nucleotide residues, whereas the full coding sequence or cDNA should be at least 993 nucleotide. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if

only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-15 are directed to all possible crystals of CatS from any biological source having at least 90% or 95% identity to SEQ ID NO: 1 as well as any crystal obtained from SEQ ID NO: 1 (claims 1-8). Claims 9-15 are directed to a method of crystallizing said CatS to produce any crystal. The specification, however, only provides a single representative species of these crystals and method of crystallization of, presumably, SEQ ID NO: 3, a tetragonal crystal in space group $P4_122$ with unit cell dimensions a = b = 85.159 Angstrom, c = 152.18 Angstrom obtained by the micro sitting drop method under the single set of crystallization conditions cited in paragraph 191, at page 48 of the specification. There is no disclosure of any particular relationship between the primary structure of the polypeptide and the crystallization conditions. The primary amino acid sequence of the polypeptide, which produced the crystal disclosed in the specification, is not apparent. It is presumed to be SEQ ID NO: 3, which includes the His-tag. Also, it is noted that the crystal described in the specification contained an inhibitor of CatS called E-64 without identifying E-64 with the appropriate chemical name or structure. Thus, the specification fails to teach the crystallization of wild-type CatS of SEQ ID NO: 1, or 90% or 95% homologues thereof, which contains at least additional 113 amino acid residue at the N-terminus of SEQ ID NO: 3. Also, the specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the cell dimensions and the

space group of claims cited in claims 5 and 6, for which no predictability of structure is apparent. In addition, the specification fails to teach any other set of condition, which produced a suitable crystal for structure determination by the X-ray diffraction method. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-15 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals comprising a having at least 90%, 95%, or 100% sequence homology to SEQ ID NO: 1. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any method to obtain any crystal comprising a protein in which at least a portion having 90%, 95%, or 100% sequence homology to SEQ ID NO: 1 and the crystal capable of diffracting X-ray to a resolution of 3 Angstroms. The specification provides guidance and examples in the form of an assay to crystallize, presumably, the complex of E-64 with the polypeptide of SEQ ID NO: 3, which is a C-terminal fragment of SEQ ID NO: 1 containing residues 113-331 and the His-tag at C-terminus, (see examples 1 and 2, and Figure 1). While molecular biological techniques and genetic manipulation to make any protein are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of proteins and their complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form is highly unpredictable. The skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants or fragments might be crystallizable. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success

in is extremely low. The amount of experimentation to identify a crystallization condition of CatS proteins from any biological source or their cystallizable mutants and fragments, and identify a crystal suitable for structure determination by X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions and mutants or fragment which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact amino acid sequence of the variant or fragment of CatS, and the crystallization conditions including any inhibitor or stabilizer added that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/63115 [Schneider *et al.* ('969)].

The '115 document teach CatS protein and the nucleic acid encoding the same in Table 1 at page 15. The amino acid sequence at page 15 of the '115 document is identical to the amino acid sequence of SEQ ID NO: 1 (claim 16). It should be noted that claim 17 is directed to CatS of SEQ ID NO: 1 expressed from a partial nucleic acid sequence. Since the claim is directed to a particular protein and the structure of the protein would not be affected by the structure of the nucleic acid as long as the nucleic acid encodes SEQ ID NO: 1, the prior art read on claim 17.

Claim 18 is allowed over the prior art of record.

The following references are qualified prior art against this application, but were not utilize because the prior art is directed to a crystal of the mature CatS comprising about 217 amino acids resides. In contrast, the instant claims is directed to the full-length 331 amino acid residues of SEQ ID NO: 1, which comprise the pre-pro region. Claim 18 is novel becuase it contains an isoleucine residue, which is not part of the mature enzyme at the N-terminus.

(1) McGrath *et al.* Protein Science (1998), 7, pages 1294-1302.

(2) Lamers *et al.* Us 2003/0143714 A1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Examiner
Art Unit 1656